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Health and Environmental Effects Profile for Pebulate

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR PEBULATE

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16. ABSTRACT

The Health and Environmental Effects Profile for pebulate was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Pebulate has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for pebulate is 5×10^{-2} (mg/kg bw/day) for oral exposure.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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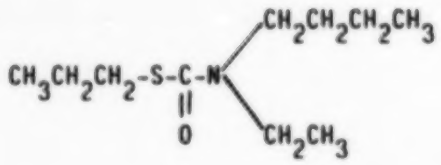
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
GSH	Glutathion
i.p.	Intraperitoneal
LD_{50}	Lethal dose to 50% of recipients
LD_{Lo}	Lowest lethal dose
LC_{50}	Lethal dose to 50% of recipients
MTD	Maximum tolerable dose
ppm	Parts per million
s.c.	Subcutaneous

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Pebulate is the common name for S-propyl butylethylthiolcarbamate. It is also known as S-propyl butylethylcarbamothioate. This compound was introduced into the market in 1954 under the code number 'R-2061' and has a trade name of Tillam (BCPC, 1977). The structure of pebulate is depicted below:



The molecular formula is $C_{10}H_{21}NOS$ and the molecular weight is 203.35. The Chemical Abstract Service (CAS) Registry Number for this compound is 1114-71-2.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Pebulate is a clear, amber to yellow liquid with an aromatic odor (BCPC, 1977; Ouellette and King, 1977). Some of the physical properties are listed below:

Physical Property		Reference
Boiling Point:	142.5°C at 20 mm Hg	BCPC, 1977
Vapor Pressure:	0.35×10^{-3} mm Hg at 25°C	Ouellette and King, 1977
Density of 20°C:	0.956 g/cm³	BCPC, 1977
Solubility in water:	60 mg/ℓ at 20°C 92 ppm at 20°C	BCPC, 1977; Kenaga, 1980; Ouellette and King, 1977; Smith and Fitzpatrick, 1970.
Soil sorption coefficient:	460-719	Kenaga, 1980; Reinbold et al., 1979.

Pebulate is also miscible with acetone, benzene, 2-propanol, kerosine, methanol and toluene. It is stable in basic solutions and is non-corrosive (BCPC, 1977).

1.3. PRODUCTION DATA

Pebulate is prepared by the reaction of butylethylamine with phosgene to give butylethylcarbamoyl chloride, which is further reacted with propane-1-thiol (BCPC, 1977). It is produced by the Stauffer Chemical Company in Cold Creek, AL (SRI, 1983; Ouellette and King, 1977). The United States production data for this compound were not available from the sources listed in the Appendix.

1.4. USE DATA

Pebulate is used as a pre-emergent herbicide to control broad-leaf weeds, grasses and nut sedges in sugar beets, tomatoes and transplanted tobacco (BCPC, 1977; Ouellette and King, 1977).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. SOIL

The fate and transport of pebulate in the soil has been well studied. Smith and Fitzpatrick (1970) determined that pebulate was resistant to chemical hydrolysis (see Section 2.3.). Therefore, it is unlikely that hydrolysis will be a significant factor in determining the fate of this compound. Casida et al. (1975) found that when S-[1-^{14}C]propyl-labeled pebulate was exposed to sunlight for 16 hours on silica gel plates, trace levels of sulfoxides, but no sulfones, were detected after 15 minutes and increased with exposure time. Photodecomposition of ^{14}C-pebulate was found to increase when sensitized with benzophenone, but more dramatically with anthraquinone. Four hours of exposure to sunlight in the presence of anthraquinone yielded no unchanged pebulate, small amounts of pebulate sulfoxide and some unidentified products.

Available data indicate that soil microorganisms contribute significantly to the disappearance of pebulate when incorporated into the soil (Kaufman, 1967). The species of microorganisms capable of degrading pebulate have not yet been identified; however, the probable degradation pathway has been described as involving hydrolysis at the ester linkage, with subsequent formation of a mercaptan, a secondary amine and CO_2. The mercaptan could then be converted to an alcohol by transthiolation and further oxidized to an acid prior to entering the metabolic pool (Kaufman, 1967).

The degree of degradation of pebulate in the soil may depend on the nature of the soil. For example, in soils with a moderate adsorptive capacity, herbicides are subjected to significant degradation by microorganisms (Koren et al., 1968). The half-life of pebulate in two soils (Regina heavy clay and Weyburn loam) was estimated as 2-3 months by Smith and Fitzpatrick (1970).

The two processes that control the transport of pebulate in the soil are volatilization and leaching. The sorption of pebulate to soils, which influences both processes, has been studied by Harris (1967) and Koren et al. (1968, 1969). The degree of adsorption of a herbicide to soil particles is directly correlated with the content of organic matter (Koren et al., 1969). The stronger the adsorption of a herbicide to soil particles, the less likely its chance for volatilization. Whether incorporated into soil or adsorbed on the surface, vapor loss from moist soils occurs more rapidly than from dry soils (Kaufman, 1967; Gray and Weierich, 1968a; Koren et al., 1969). In addition, Gray and Weierich (1968a) reported that increasing the temperature from 32-100°F had little effect on the vapor loss of pebulate from the surface of the soil. Koren et al. (1969) measured the rate of vaporization of pebulate from five types of soils and found that regardless of the soil type, a relationship exists between the volatility and the vapor pressure of the herbicide. Infiltration into the soil appeared to be very important under the controlled conditions of this study, whereas under field conditions, the ability of the herbicide to "escape" volatilization is more likely to be dependent on the time needed for drying of the spray rather than the infiltration capacity of the soil. Therefore, it can be qualitatively stated that volatilization will contribute to the transport of this herbicide from moist soils and from soils with low organic matter.

Leaching is another important factor that will affect the transport of a herbicide in the soil (Gray and Weierich, 1968b). The leaching of pebulate from soil is directly related to its water solubility and inversely related to the organic matter content of the soil (Koren et al., 1969). Gray and Weierich (1968b) studied the depth of leaching of pebulate in five types of soils and found that it decreased as the clay and organic matter content of

the soil increased. Pebulate out did not move of the treated zone of a peat soil containing 34.6% organic matter and 17.6% clay. Koren et al. (1969) used five soils with clay contents of 2-28.8% and organic matter contents of 0.52-51.8%, and observed increasing rates of leaching by pebulate with decreasing organic matter content.

Harris (1967) described a system to evaluate relative mobility of 28 herbicides in the soil. Pebulate was applied at the rate of 8 pounds/acre to two soils, Hagerstown silty clay loam (4.3% organic matter and 30% clay) and Lakeland sandy loam (3.3% organic matter and 10% clay). Using fresh weights of oats as a bioassay, mobility factors of 2.3 and 2.2 were calculated for pebulate in the two soils, respectively. The extreme values of 1.0 for no movement and 6.0 for maximum movement were arbitrarily assigned for comparative purposes.

2.2. AIR

Although few data regarding the fate and transport of pebulate in the atmosphere were available, some inferences can be made based on physical properties. The two likely routes of entry of this herbicide into the atmosphere are spray drift during application and volatilization from the soil. The fate of pebulate in the atmosphere will depend upon its reactions with O_3, NO_x and free radicals (e.g., RO•, O• and RO_2•), and its ability to undergo photolysis. Although no information was encountered on the reaction of pebulate with atmospheric reactants in the literature searched, there are limited data on its photolysis.

DeMarco and Hayes (1979) studied the photodegradation of pebulate in hexane following exposure of 260 mℓ of solution to a medium pressure mercury lamp. From an initial concentration of 0.6 M, the herbicide was degraded at an initial rate of 0.02 moles/ minute, and was unaffected by

variation of the herbicide concentration (100-1000 ppm) or changes in temperature (10-30°C); however, it is difficult to extrapolate these results to predict the photochemical reactivity of pebulate in the atmosphere.

No information was encountered which described the transport of pebulate in the atmosphere. Based on the soil sorption coefficient (K_{oc}) of 630 (Kenaga, 1980), it is likely that the compound may exist in the atmosphere in the particulate-sorbed phase. Considering the solubility of this compound (60-92 mg/ℓ), it is possible that the particulate-sorbed compound may be removed from the atmosphere by dry or wet deposition.

2.3. WATER

The fate and transport of pebulate in aquatic media have not been well studied. Casida et al. (1975) reported that pebulate was not detectably hydrolyzed during 24 hours in distilled water or in an aqueous medium with a pH of 10. Similarly, Smith and Fitzpatrick (1970) found that pebulate in 10N NaOH solution underwent little hydrolysis after 1 hour at 95°C, and only 50% was hydrolyzed after 1 hour at 95°C in 18N sulfuric acid. Therefore, it is unlikely that hydrolysis will affect the fate of pebulate in an aqueous environmental medium.

The two processes that predominate in the aquatic transport of pebulate are sorption and volatilization. In a Russian abstract, Popovich (1982) reported that following irrigation, 1.6 mg/m³ of pebulate was detected in the air over rice paddies; however, the original concentration in water or soil was not given. As stated previously, volatilization will occur more readily from moist surfaces than dry surfaces. The absorption of pebulate by soils from aqueous solutions was determined to be 16.8-100% for seven soils tested (Koren et al., 1969). These results indicated that sorption onto suspended particulate matter may play a significant role in determining the transport of this compound in aquatic media.

Kenaga (1980) predicted a BCF of 35-61 for pebulate from binary regression equations. Therefore, this compound is not expected to bioaccumulate significantly in aquatic species.

3. EXPOSURE

No monitoring information was encountered in STORET. Frank et al. (1979) reported that pebulate was detected at levels of 1.1-10.0 µg/ℓ in three wells in Ontario, Canada. Contamination was attributed to storm water runoff. Pebulate was detected in the air over rice paddies 3 days after application at levels of 1.6 mg/m³ (Popovich, 1982).

4. PHARMACOKINETICS

4.1. ABSORPTION

Data relating specifically to the absorption of pebulate were not located in the available literature; however, some information was obtained from metabolism studies. Male Swiss-Webster mice were administered in an 80% ethanol solution by gavage 100 mg/kg S-[1-^{14}C]propyl-labeled pebulate. Within 24 hours, 38-39% of the radiolabel was expired as $^{14}CO_2$ and other volatile compounds, and 56-61% was excreted in the urine (Casida et al., 1975). In an abstract of a Russian study, Aleksandrova and Klisenko (1978) reported that metabolites of pebulate were detected in the tissues of rats from 0.5-24 hours, and in the blood for 2 days following ingestion of an unspecified dose of pebulate. These studies suggested that pebulate was rapidly absorbed from the gastrointestinal tract of rats and mice.

4.2. DISTRIBUTION

In an abstract of a study from the Russian literature, Aleksandrova and Klisenko (1978) presented results which stated that metabolites of pebulate were detected in the tissues of rats from 0.5-24 hours and in the blood for 2 days after ingestion of an unspecified dose. No other information on the distribution of this compound was encountered in the available literature.

4.3. METABOLISM

Casida et al. (1974, 1975) studied the sulfoxidation of pebulate by Swiss-Webster mice in vivo and by mouse liver microsomes in vitro. Preparations of S-[1-^{14}C]propyl-labeled pebulate or pebulate sulfoxide were administered in 80% ethanol solution by gavage at a level of 100 mg/kg to male mice. The proportion of volatile and urinary products was almost identical from ^{14}C-pebulate and ^{14}C-pebulate sulfoxide. Within 48 hours, the recoveries of ^{14}C from pebulate and pebulate sulfoxide were

38-39% as $^{14}CO_2$ or other volatile products in the expired air, and 56-61% as metabolites in the urine. The sulfoxide, a proposed transient metabolic intermediate of pebulate in mammalian systems, was detected in the livers of mice within 10 minutes following i.p. injection of 1 mmole/kg of pebulate, but was not detected 60 minutes after treatment (Casida et al., 1974). Sulfones were not detected as metabolites in the liver of mice, but sulfones were not expected to persist because they are hydrolytically unstable (Casida et al., 1974, 1975).

Mouse liver microsomes and NADPH metabolized ~45%, of S-[1-^{14}C]propyl-labeled pebulate after a 1 hour incubation period. Pebulate sulfoxide was detected as the major metabolite (23%). Five organosoluble metabolites (8%) and water soluble metabolites (14%) were also formed. The extent of pebulate metabolism increased to ~70% when the soluble enzymes and glutathione (GSH) were added to the incubation system. A volatile mercaptan was also liberated and the sulfoxide recovery decreased (Casida et al., 1975). These results suggested that the reaction of GSH with pebulate sulfoxide results in the cleavage of the carbonyl bond by GSH or GSH S-transferase (or transferases) at the carbonyl group, thus liberating either the mercaptan or sulfonic acid.

4.4. EXCRETION

Mice expired ~38-39% of the orally administered 100 mg/kg dose of ^{14}C-pebulate as $^{14}CO_2$ or other volatile compounds within 24 hours (Casida et al., 1975). In addition, 56-61% of the label appeared in the urine. No other information on the excretion of this compound was found in the available literature.

5. EFFECTS

5.1. CARCINOGENICITY

Only one study (Bionetics Research Laboratories, 1968; Innes et al., 1969) describing the potential carcinogenicity of pebulate was available. Two hybrid strains of male and female mice ($B6C3F_1$ and $B6AKF_1$) were administered 100 mg/kg/day pebulate in corn oil MTD (calculated from the average body weight of mice at the start of the study and corrected for weight gain) by gavage from day 7-28 of age, after which pebulate was given in the diet at a level of 323 ppm for ~18 months. Negative controls consisted of untreated and vehicle treated mice of both sexes and both strains. At 80 weeks of age, the mice were sacrificed and necropsied. The total tumor incidence for $B6C3F_1$ mice was 1/16 treated males and 2/18 treated females compared with 22/79 control males and 8/87 control females. Only pulmonary adenomas and hepatomas were found in treated males at incidences of 1/16 for each type of tumor compared with 5/79 (pulmonary adenoma) and 8/79 (hepatoma) for the control group. For strain $B6AKF_1$, the total tumor incidences were 2/15 for treated males and 2/15 for treated females, compared with 16/90 control males and 7/82 control females. Only pulmonary adenomas were found at incidences of 2/15 for treated males and 2/15 for treated females compared with 9/90 control males and 3/82 for control females. Tumor incidences in treated groups were not considered to be significantly different from incidences in the corresponding control groups.

$B6C3F_1$ and $B6AKF_1$ mice (18/sex/strain) were administered a single s.c. injection of 10 mg/kg pebulate in corn oil on the 28th day of age and sacrificed after 18 months (Bionetics Research Laboratories, 1968). In $B6C3F_1$ mice, the incidence of reticulum cell sarcoma was 3/18 in treated males compared with 8/141 for the control males. Pulmonary adenoma occurred

at an incidence of 2/18 treated males compared with 10/141 control males, and hepatomas occurred in 3/18 treated males compared with 9/141 control males. Tumor incidences among treated $B6AKF_1$ mice were even lower than among treated $B6C3F_1$ mice. Differences in tumor incidences between treated and control groups were not considered to be statistically significant for either strain of mice.

5.2. MUTAGENICITY

Pebulate was not shown to induce reverse mutations in the spot test with any of eight strains of histidine-dependent mutants of Salmonella typhimurium; the S-9 metabolic activating fraction was not employed (Andersen et al., 1972). Shirasu et al. (1976) also reported that pebulate failed to induce mutations in the absence of metabolic activation in spot tests with auxotrophic strains of Escherichia coli (WP2) and four strains (TA1535, TA1536, TA1537 and TA1538) of histidine-dependent Salmonella typhimurium. Negative results were obtained in the rec-assay with repair deficient and proficient strains of Bacillus subtilis tested in the absence of a metabolic activating fraction (Shirasu et al., 1976).

5.3. TERATOGENICITY

No information on the teratogenic potential of pebulate was located in the available literature.

5.4. OTHER REPRODUCTIVE EFFECTS

Voitenko and Medved, (1973) reported that pebulate, administered orally in dosages of 3.6 mg/kg/day to young rats for 2 months, failed to produce any gonadotoxic effects.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

The only available data concerning the toxic effects of chronic and subchronic exposures to pebulate were contained in abstracts of Russian

studies. Olefir (1973b) administered orally to rats unspecified doses that corresponded to 1/20 of the LD_{50} values 5 times/week for 4.5 months. Observations included inhibition of nonspecific immunobiological reactivity of the animals for up to 2 months after the herbicide was discontinued including a decrease in the resistance of the treated rats to a staphylococcal infection. Effects of daily oral doses of 56 mg/kg of pebulate to rats for 16 weeks resulted in respective decreases of 30 and 63% in liver and brain tissue respiration, a 34% decrease in cytochrome activity and a decrease in the activities of succinic dehydrogenase, cytochrome C oxidase and anaerobic glycolysis. Accumulation of lactic and pyruvic acids in the blood was also observed (Proklina-Kaminskaya, 1969). Similar effects were observed in rats by Kaminskaya (1969) following daily oral administration of 112.5 mg/kg for 4 weeks. Administration of 27 mg/kg of pebulate (5% of LD_{50}) to rats every other day for 34 days caused "delay of the development of conditioned reflexes, their rapid extinction and slow restoration after extinction" (Pushchina, 1969).

5.6. OTHER RELEVANT INFORMATION

Oral LD_{50} values for pebulate have been reported as 1120 mg/kg in the rat and 1652 mg/kg in mice; LD_{50}s of 1125 and 713 mg/kg for unknown routes of administration were also reported for the rat and for an unspecified mammal, respectively (NIOSH, 1983). An i.p. LD_{50} of 145 mg/kg was reported for mice (Casida et al., 1975). Inhalation LD_{50}s for mice, rats and cats were reported as 750, 1125 and 750 mg/kg, respectively (Voitenko et al., 1972). An oral LD_{Lo} of 500 mg/kg for humans was also reported (NIOSH, 1983).

Olefir (1973a) investigated the acute toxicity of pebulate and observed immune suppression in rats for >2 months following administration of an

unspecified maximum tolerable dose (MTD) (Olefir, 1973a). Hunt (1971) demonstrated that 250 mg/kg fed daily to sheep for up to 15 days, and 100 mg/kg fed to cattle for up to 7 days, resulted in mild congestion in the spleen, adrenal glands, thyroid glands and lung parenchyma, acute toxic tubular nephritis, hepatic damage pneumonitis, and increased blood urea nitrogen levels. Rusyaeva and Rusyaev (1969) reported that minimum toxic doses of pebulate produced Heinz body induction in red blood cells of an unspecified animal. Concentrations of 350 µg/mℓ of pebulate inhibited amino acid incorporation in HeLa cells in vitro (Myhr, 1973).

Voitenko et al. (1967) reported that a single MTD of pebulate administered orally to rats decreased the activities of RNase and DNase in the liver and spleen, and disrupted the normal function of the thyroid gland. Following administration of a single dose of 750 mg/kg of pebulate to male rats, endogenous respiration was increased by 44%, cytochrome oxidase activity increased by 30% and succinate dehydrogenase activity was increased by 35% (Proklina-Kaminskaya, 1968). Similar results were obtained by Kaminskaya (1969) following administration of a single oral dose of 750 mg/kg of pebulate to rats (i.e., increases in tissue respiration and in the activities of succinate dehydrogenase and cytochrome oxidase, especially in the liver). In contrast, an unspecified "subtoxic" dose of pebulate resulted in a 17% decrease in endogenous respiration, 24% decrease in cytochrome oxidase activity, and a 17% decrease in succinate dehydrogenase activity (Proklina-Kaminskaya, 1968).

One study was located relating to human exposure and epidemiological investigations. Swift (1976) reported the occurrence of eye irritation in workers exposed to spray drift during application of pebulate.

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

Acute toxicity tests of pebulate have been conducted with five species of freshwater invertebrates and four species of marine animals. The 48-hour LC_{50} values for four species of freshwater snails ranged between 36 and 66 mg/ℓ (Nishiuchi and Yoshida, 1972). The 96-hour LC_{50} value for a freshwater amphipod, Gammarus fasciatus, was 10 mg/ℓ (Sanders, 1970). Butler (1963) reported similar 48-hour LC_{50} values for two marine fish species; 6.25 mg/ℓ for mullet, Mugil curema, and 7.78 mg/ℓ for longnose killifish, Fundulus similis. In a later study, Butler (1964) reported that 1.0 mg/ℓ had no effect on white shrimp, Penaeus setiferus, after 48 hours of exposure and caused a 20% decrease in shell growth of oysters, Crassostrea virginica, during a 96-hour exposure period.

6.2. CHRONIC TOXICITY

Pertinent data regarding the chronic toxicity of pebulate on aquatic animals were not located in the available literature.

6.3. PLANT EFFECTS

The only information regarding the effects of pebulate on aquatic plants was provided by Butler (1963) who reported that the productivity (^{14}C fixation) of a natural mixed phytoplankton assemblage was reduced by 23.8% during 4 hours of exposure to 1.0 mg/ℓ.

6.4. RESIDUES

Pertinent data regarding pebulate residues in aquatic organisms were not located in the available literature. However, based on a predicted BCF of 35-61 (see Section 2.3.), this compound is not expected to bioaccumulate significantly in aquatic organisms.

6.5. OTHER RELEVANT INFORMATION

Other relevant information concerning the aquatic effects of pebulate was not located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

No existing guidelines or standards were located for pebulate in the available literature. Two Russian studies were located which reported calculation of a maximum permissible level in soil of 0.35 mg/kg of pebulate based on the known values for 18 commonly used pesticides (Medved et al., 1979), and a maximum permissible concentration in air of 1 mg/m^3 (Voitenko et al., 1972).

7.2. AQUATIC

Guidelines or standards for the protection of aquatic organisms from the toxic effects of pebulate were not located in the available literature.

8. RISK ASSESSMENT

Pebulate does not appear to be carcinogenic, but it has been tested in only one species. Pebulate was evaluated for carcinogenicity by Bionetics Research Laboratories (1968). No evidence of increased tumor incidence was reported in mice administered pebulate by gavage at 100 mg/kg from days 7-28 of age and thereafter at dietary concentrations of 323 ppm until 532 days of age, or in mice 18 months after subcutaneous administration of a single dose of 10 mg pebulate/kg. Negative results were obtained for pebulate in in vitro mutagenicity assays with bacteria (Andersen et al., 1972; Shirasu et al., 1976). These assays were performed without an exogenous metabolic activating system. No information regarding the potential teratogenicity of pebulate was located in the available literature.

The only available information regarding the toxic effects of chronic and subchronic exposures of pebulate was contained in abstracts of Russian studies. Olefir (1973b) reported that oral administration of 1/20 of the LD_{50} value, 5 times a week for 4.5 months, inhibited nonspecific immunobiological reactivity in rats. Daily doses of 56 mg/kg of pebulate, administered orally to rats for 16 weeks, decreased liver and brain tissue respiration, cytochrome activity, and the activities of succinic dehydrogenase, cytochrome C oxidase and anaerobic glycolysis. Accumulation of lactic and pyruvic acids in the blood was also observed (Proklina-Kaminskaya, 1969). Similar effects were observed in rats by Kaminskaya (1969) following daily oral administration of 112.5 mg/kg for 4 weeks. These data are not an adequate basis for the derivation of an ADI value for pebulate.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews other animal data from which an ADI of 0.05 mg/kg bw/day, or 3.5 mg/day for a 70 kg man, was derived. The ADI was based on a NOEL of 5 mg/kg bw/day in rats in subchronic feeding studies and an uncertainty factor of 100 (10 to account for interspecies extrapolation and 10 for protection of unusually sensitive individuals within the human population). The LOAEL in these studies, 20 mg/kg bw/day, was associated with anticoagulant effects.

9. REFERENCES

Aleksandrova, L.G. and M.A. Klisenko. 1978. Kinetics of the accumulation and elimination of thiocarbamine pesticides from warm-blooded animals. Gig. Sanit. 6: 101-103. (Rus.) [Taken from Chem. Abstr. 89(9)71801k].

Andersen, K.J., E.G. Leighty and M.T. Takahaski. 1972. Evaluation of herbicides for possible mutagenic properties. J. Agric. Food Chem. 20: 649-656.

Bionetics Research Laboratories, Inc. 1968. Evaluation of carcinogenic, teratogenic and mutagenic activities of selected pesticides and industrial chemicals. Vol. I. Carcinogenic Study Rep. No. NCI-DCCPC 61973-1-1. Bethesda, MD. NTIS PB 223-159.

BCPC (British Crop Protection Council). 1977. Pesticide Manual issued by: BCPC, England, 5th ed. Boots Company, Ltd., Nottingham, England. p. 593.

Butler, P.A. 1963. Commercial fisheries investigations. In: A Review of Fish and Wildlife Investigations During 1961 and 1962. U.S. Fish Wildl. Serv. Circ. 167. U.S. Fish Wildl. Serv., U.S. Dept. Interior, Washington, DC. p. 11-25.

Butler, P.A. 1964. Commercial fishery investigations. In: Pesticide-wildlife studies, 1963: A Review of Fish and Wildlife Service Investigations During the Calendar Year. Fish Wildl. Serv. Circ. 199. U.S. Fish Wildl. Serv., U.S. Dept. Interior, Washington, DC. p. 5-28.

Casida, J.E., R.A. Gray and H. Tilles. 1974. Thiocarbamate sulfoxides. Potent, selective and biodegradable herbicides. Science. 184(4136): 573-574.

Casida, J.E., E.C. Kimmel, H. Ohkawa and R. Ohkawa. 1975. Sulfoxidation of thiocarbamate herbicides and metabolism of thiocarbamate sulfoxides in living mice and liver enzyme systems. Pestic. Biochem. Physiol. 5(1): 1-11.

DeMarco, A.C. and E.R. Hayes. 1979. Photodegradation of thiocarbamate herbicides. Chemosphere. 8(5): 321-326.

Frank, R., G.J. Sirons and B.D. Ripley. 1979. Herbicide contamination and decontamination of well water in Ontario, Canada, 1969-78. Pestic. Monit. J. 13(3): 120-127.

Gray, R.A. and A.J. Weierich. 1968a. Behavior and persistance of thiocarbamate herbicides in soils under different environmental conditions. Proc. 9th Brit. Weed Control Conf. p. 94-101.

Gray, R.A. and A.J. Weierich. 1968b. Leaching of five thiocarbamate herbicides in soils. Weed Sci. 16(1): 77-79.

Harris, C.I. 1967. Movement of herbicides in soil. Weeds. 15(3): 214-216.

Hunt, L.M., B.N. Gilbert, J.S. Palmer and R.L. Younger. 1971. Effects of a thiocarbamate herbicde compound (pebulate) on magnesium/calcium ratio and blood urea nitrogen levels in exposed sheep and cattle. Bull. Environ. Contam. Toxicol. 6(3): 263-272.

Innes, J.R.M., B.M. Uuand, M.G. Valerio, et al. 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. J. Natl. Cancer Inst. 42: 1101-1114.

Kaminskaya, T.L. 1969. Tissue oxidative processes in poisoning with pesticides: Derivatives of carbamic, thiocarbamic and dithiocarbamic acids. Vrach. Delo. 6: 101-103.

Kaufman, D.D. 1967. Degradation of carbamate herbicides in soil. J. Agric. Food Chem. 15: 582-591.

Kenaga, E.E. 1980. Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals. Ecotoxicol. Environ. Safety. 4: 26-38.

Koren, E., C.L. Foy and F.M. Ashton. 1968. Phytotoxicity and persistence of four thiocarbamates in five soil types. Weed Sci. 16(2): 172-175.

Koren, E., C.L. Foy and F.M. Ashton. 1969. Adsorption, volatility and migration of thiocarbamate herbicides in soil. Weed Sci. 17(2): 148-153.

Medved, L.I., E.I. Spynu and R.E. Sova. 1979. Determination of hygenic standards for pesticides in soils by calculation. Gig. Sanit. 11: 22-54. (Rus.) (Taken from PESTAB 80/1060).

Myhr, B.C. 1973. Screen for pesticide toxicity to protein and RNA synthesis in HeLa cells. J. Agric. Food Chem. 21(3): 362-367.

NIOSH (National Institute for Occupational Safety and Health). 1983. RTECS (Registry of Toxic Effects of Chemical Substances). Online, February, 1983.

Nishiuchi, Y. and K. Yoshida. 1972. Toxicities of pesticides to some freshwater snails. Bull. Agric. Chem. Inspec. Station. 12: 86-92.

Olefir, A.I. 1973a. Effect of acute poisoning with carbamine pesticides on immunological reactivity. Vrach. Delo. 4: 138-141. (Rus.) (Taken from Chem. Abstr. 79:122419v).

Olefir, A.I. 1973b. Effect of chronic intoxication with carbamine pesticides on immunobiological reactivity and resistance to infection. Vrach. Delo. 8: 137-141. (Rus.) (Taken from Chem. Abstr. 79:74595a).

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY. p. 345.

Popovich, N.A. 1982. Detoxication period before onset of work after application of carbamates and thiocarbamates under conditions of irrigation. Gig. Tr. Prof. Zabol. 2: 40-42. (Rus.) (Taken from Chem. Abstr. 96: 917196s).

Proklina-Kaminskaya, T.L. 1968. Effect of carbamates on tissue respiration and the activity of cytochrome oxidase, and succinate dehydrogenase in rat liver. Farmakol. Toksikol. (Kiev). 4: 153-155. (Rus.) (Taken from Chem. Abstr. 71:69655a).

Proklina-Kaminskaya, T.L. 1969. Effect of continuous exposure to pesticides (carbamates, thiocarbamates and dithiocarbamates) on oxidative processes in animals. Gig. Tr. 1: 91-94. (Rus.) (Taken from Chem. Abstr. 72:65787t).

Pushchina, I.K. 1969. Effect of herbicidal thiocarbamic acid derivatives on conditioned reflex activity of rats during multiple administration. Razv. Sovrem. Probl. Gig. BSSR. p. 65-68. (Rus.) (Taken from Chem. Abstr. 74:109799w).

Reinbold, K.A., T.T. Hassett, J.C. Means and W.L. Banwott. 1979. Adsorption of energy-related organic pollutants: A literature review. Illinois Univ. at Urbana-Champaign. p. 180. EPA/600/3-79/086, PB 80-105117.

Rusyaeva, L.N. and V.A. Rusyaev. 1969. Diagnostic importance of Heinz bodies in poisoning with some chemical poisons. Zdravookhr. Beloruss. 15(8): 64-67. (Rus.) (Taken from Chem. Abstr. 72:42184e).

Sanders, H.O. 1970. Toxicities of some herbicides to six species of fresh water crustaceans. J. Water Pollut. Contr. Fed. 42(8, Pt. 1): 1544-1550.

Shirasu, Y., M. Moriya, K. Kato, A. Furuhashi and T. Kada. 1976. Mutagenicity screening of pesticides in the microbial system. Mutat. Res. 40: 19-30.

Smith, A.E. and A. Fitzpatrick. 1970. Loss of five thiolcarbamate herbicides in nonsterile soils and their stability in acidic and basic solutions. J. Agric. Food Chem. 18(4): 720-722.

SRI, Directory of Chemical Producers. 1983. SRI International, Menlo Park, CA.

Swift, J.E. 1976. Organophosphate exposure from agricultural usage. ORD, U.S. EPA, Washington, DC. EPA-600/1-76-025. p. 264-290.

Voitenko, G.A., I.A. Anina, M.B. Rappoport, T.U. Dyadicheva and V.Yu. Kassin. 1967. Mechanism of the action of pesticides which are carbamic thio- and dithiocarbamic acid derivatives. Vop. Gig. Toksikol. Pestits. p. 110-117. (Rus.) (Taken from Chem. Abstr. 74:98742u).

Voitenko, G.A., T.L. Kaminskaya and V.N. Karpenko. 1972. Experimental data for substantiating the maximal permissible concentration of Tillam in the air of a working zone. Gig. Sanit. 50(8): 104-105. (Rus.) (Taken from Chem. Abstr. 78:12305b).

Voitenko, G.A. and I.L. Medved. 1973. Effect of some thiocarbamates on the generative function. Gig. Sanit. 7: 111-114. (Rus.) (Taken from Chem. Abstr. 78:12305b).

APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
EPCASR
Chemical Industry Notes

Most of these searches were conducted in February, 1983; a few were conducted March-May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. TLVs: Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1982. Documentation of the Threshold Limit Values for Chemical Substances in Work Air. Cincinnati, OH. 94 p.

Bruin, P., G.J. Bergen and J.J. Desta, Ed. 1980. Handling Chemicals Safely, 2nd ed. Dutch Assoc. of Safety Experts, Dutch Chemical Industry Assoc., and Dutch Safety Institute, The Netherlands. 1013 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. 2879-3816 p.

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Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. 2879-3816 p.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. 3817-5112 p.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

Muir, G.D., Ed. 1977. Hazards in the Chemical Laboratory, 2nd ed. The London Chemical Society, London. 473 p.

NTP (National Toxicology Program). 1982. Carcinogenesis Testing Program. Chemicals on Standard Protocol. Management Status. Report date: December 31, 1982.

Proctor, N.H. and J. P. Hughes. 1978. Chemical Hazards of the Workplace. J.B. Lippincott Co., Philadelphia, PA. 533 p.

Sax, I.N. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

U.S. EPA. 1980. Chemical Hazard Information Profile: Vinyl Bromide. In: TSCA Chemical Assessment Series. Chemical Hazard Information Profiles (CHIPs). August 1976-1978. EPA 560/11-80-011.